



Cardiovascular biomarkers in preeclampsia at triage

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Abstract: INTRODUCTION: to investigate the ability of cardiovascular plasma biomarkers to identify imminent preeclampsia (PE) among pregnant women at triage. MATERIAL AND METHODS: C-terminal pro-arginine vasopressin (copeptin), C-terminal pro-endothelin-1 (CT-proET-1), mid-regional pro-adrenomedullin (MR-proADM), and mid-regional pro-atrial natriuretic peptide (MR-proANP) were prospectively measured in pregnant women presenting at the obstetrical triage units of the University Hospitals of Basel and Zurich, Switzerland. Logistic regression and receiver operating characteristics (ROC) analysis was used to assess and quantify the predictive ability of cardiovascular biomarkers. RESULTS: Of the 147 included women, 27 (18.4%) were diagnosed at admission with PE. All biomarker levels were significantly higher in participants with PE as compared to controls. However, only MR-proANP, MR-proADM and CT-proET-1 were significant and independent predictors of PE, after taking into account the effect of various clinical confounders. The area under the ROC curve (AUC) was 0.62 (95% confidence interval 0.50-0.73) for copeptin, 0.64 (0.52-0.76) for MR-proADM, 0.71 (0.61-0.82) for CT-proET-1, and 0.83 (0.73-0.92) for MR-proANP. The combination of MR-proANP and MR-proADM resulted in the highest diagnostic performance (AUC 0.88; 0.79-0.96). DISCUSSION: Assessment of the cardiovascular plasma biomarkers MR-proANP and MR-proADM holds promise to support diagnosis of PE at triage.

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Cardiovascular Biomarkers in Preeclampsia at Triage

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Key Words

Biomarker · Preeclampsia · At triage · Vasoactive peptides · Pregnancy · Obstetrics · Cardiovascular

Abstract

Introduction: To investigate the ability of cardiovascular plasma biomarkers to identify imminent preeclampsia (PE) among pregnant women at triage. **Material and Methods:** C-terminal pro-arginine vasopressin (copeptin), C-terminal pro-endothelin-1 (CT-proET-1), mid-regional pro-adrenomedullin (MR-proADM), and mid-regional pro-atrial natriuretic peptide (MR-proANP) were prospectively measured in pregnant women presenting at the obstetrical triage units of the University Hospitals of Basel and Zurich, Switzerland. Logistic regression and receiver operating characteristics (ROC) analysis was used to assess and quantify the predictive ability of cardiovascular biomarkers. **Results:** Of the 147 included women, 27 (18.4%) were diagnosed at admission with PE. All biomarker levels were significantly higher in participants with PE as compared to controls. However, only MR-proANP, MR-proADM and CT-proET-1 were significant and independent predictors of PE, after taking into account the effect of

various clinical confounders. The area under the ROC curve (AUC) was 0.62 (95% confidence interval 0.50–0.73) for copeptin, 0.64 (0.52–0.76) for MR-proADM, 0.71 (0.61–0.82) for CT-proET-1, and 0.83 (0.73–0.92) for MR-proANP. The combination of MR-proANP and MR-proADM resulted in the highest diagnostic performance (AUC 0.88; 0.79–0.96). **Discussion:** Assessment of the cardiovascular plasma biomarkers MR-proANP and MR-proADM holds promise to support diagnosis of PE at triage.

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Introduction

Preeclampsia (PE) is a multi-system disorder of pregnancy, which is characterized by new-onset hypertension (systolic and diastolic blood pressures of ≥ 140 and 90 mm Hg, respectively, on two occasions, at least 6 h apart) and proteinuria (protein excretion of ≥ 300 mg in a 24-hour urine collection, or a dipstick of $\geq 2+$), that develop after 20 weeks of gestation in previously normotensive women, occurs in 2–8% of pregnancies [1]. PE may occur as a consequence of an aberrant maternal inflammatory response,

including a systemic vascular dysfunction. The inflammatory reaction may lead to oxidative stress. Furthermore, oxidative stress can stimulate an inflammatory response, forming the platform for a positive feedback between the two conditions [2]. However, whereas blood biomarkers of angiogenesis are good predictors of PE [3, 4], mediators of inflammation, namely cytokines, do not indicate development of PE [5].

According to the latest report of Confidential Enquires into Maternal Deaths in the United Kingdom, the most common reason for maternal death resulting from substandard care was a failure to appropriately diagnose or manage PE [6]. Although maternal deaths resulting from PE are rare events, most of the deaths were found to be associated with substandard care, caused by a failure to recognize the signs and symptoms of this condition [7].

The standard methods to diagnose PE consist of standardized blood pressure measurement, urine analysis for the detection of proteinuria and the determination of uric acid, platelet counts and liver enzymes in the maternal blood [8]. However, the diagnostic performance of these parameters is still controversial, and they are poor predictors of either maternal or fetal complications [9]. Therefore, a reliable new diagnostic test may facilitate clinician's assessment, clinical decision and the correct identification of high-risk pregnancies at admission.

Copeptin is a stable by-product of the arginine vasopressin (AVP) synthesis and has become a widely used surrogate marker of AVP release, reflecting hemodynamic and osmoregulatory effects, as well as individual stress levels [10]. Endothelin-1 (ET-1), a potent vasoconstrictor, is secreted by endothelial cells in response to various stressors, and its secretion can be reliably estimated by measuring the carboxy-terminal portion of the ET-1 precursor (CT-proET-1) [11]. The atrial natriuretic peptide (ANP) is released into circulation with its stable by-product mid-regional pro-ANP (MR-proANP), a biomarker for cardiovascular hemodynamic stress and hypertension [12]. Adrenomedullin (ADM) and its stable by-product mid-regional pro-ADM (MR-proADM) are expressed in all organs but predominantly in vascular endothelial cells and vascular smooth muscle cells where it regulates circulation and endothelial permeability [13, 14].

In this cross-sectional prospective study, we investigated the validity of these promising biomarkers, namely copeptin, MR-proANP, CT-proET-1, and MR-proADM to accurately discriminate preeclamptic patients versus controls at triage.

Materials and Methods

This study included 147 pregnant women between 24 and 42 weeks of gestation in a prospective, cross-sectional study performed between March 2009 and July 2010 at the University Hospitals of Basel and Zurich, Switzerland. Women were eligible either if they presented or were referred to the obstetrical triage unit of both centers, for example with clinical symptoms of suspected PE or with increased risk of preterm delivery. All patients provided written informed consent.

Exclusion criteria were: (1) patients in the first and second stage of labor and with regular uterine contractions, (2) pregnant women with preexisting hypertension before 20 weeks of gestation, (3) diabetes mellitus, (4) kidney and heart disease, (5) signs of chorioamnionitis, and (6) confirmed PE before admission.

The study was approved by the institutional review boards of the University Hospital of Basel and Zürich (Ethikkommission beider Basel, EKBB 07/09, Kantonale Ethikkommission Zürich, KEK 08/09) and was carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participating patients.

Characteristics from mothers and infants were collected from the charts. In detail, from mothers: age at delivery and body mass index (BMI) before pregnancy; in pregnancy parity, singleton or twin pregnancy, gestational diabetes mellitus (GDM), and administration of any antenatal steroids for fetal lung maturation; at delivery umbilical cord artery pH. From infants: gestational age (GA), based on the ultrasonographical crown-rump length measurement at the end of the first trimester, birth weight, and Apgar scores at 5 and 10 min of life. Diagnosis of PE was subsequently established in the obstetrical triage unit of both centers, according to the definition of elevated blood pressure (≥ 140 mm Hg systolic and ≥ 90 mm Hg diastolic blood pressure) and significant proteinuria (≥ 300 mg/24 h, or $\geq ++$ in urine dipsticks). Additional parameters, such as hemolysis, thrombocytopenia, elevated liver enzymes, and/or severe intrauterine growth restriction and fetal compromise were recorded. GDM was diagnosed using a 75-gram oral glucose tolerance test in the second trimester.

After collecting blood in EDTA tubes, samples were centrifuged and plasma was frozen at -28°C . Each pro-peptide was measured in a single batch. MR-proANP (pmol/l), CT-proET1 (pmol/l), and MR-proADM (nmol/l) were measured by means of fully automated BRAHMS KRYPTOR immunofluorescent assays (B-R-A-H-M-S GmbH, part of Thermo Fisher Scientific, Hennigsdorf, Germany) and Copeptin (pmol/l) was measured with a research sandwich immunoluminometric assay (BRAHMS C-terminal pro-AVP luminescence immunoassay, BRAHMS) as described previously [15].

Continuous variables were presented as medians with range whereas categorical variables as number of cases with rates. Between-group comparisons were performed using the Mann-Whitney U test, χ^2 test, and Fisher's exact test, as appropriate. The effect of various clinical parameters on biomarkers levels was assessed by linear regression analysis after logarithmic transformation of the dependent variable. Simple and multivariable linear regression models were used to explore the unadjusted and adjusted effect of these parameters, respectively. According to good common practice, we used the term multivariable analysis as various input variables, but only one outcome parameter each time was analyzed. Multivariable logistic regression analysis was used to explore the

diagnostic value of each biomarker separately after taking into account the effect of possible clinical confounders (nullipara, singleton pregnancy, GDM, antenatal steroids, maternal age at delivery, GA at delivery). The combined effect of all biomarkers was also assessed in a separate model. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated in order to quantify the diagnostic ability of each biomarkers. A combined biomarker index consisting of the product between MR-proANP and MR-proADM, was also evaluated. A *p* value <0.05 was considered to be significant in all instances. Statistical analysis was performed with IBM SPSS version 20.0 (IBM Corp., Armonk, N.Y., USA).

Results

A total of 147 women with complete clinical and biomarker data were included in the analysis. Demographic characteristics and pregnancy outcomes are presented in table 1. Women in the PE group were enrolled on average 4.2 weeks earlier in pregnancy (mean 32.84 weeks GA, 95% CI 31.35–34.32) as compared to controls (mean 37.06 weeks GA, 95% CI 36.39–37.73), *p* < 0.001. Enrollment was done at the time point of blood sampling and was done on average 25 h before delivery (95% CI 19–32 h); in women with PE, blood sampling was 7.8 h closer to delivery (on average 18.9 h before delivery, 95% CI 8.8–29.1) than in controls (26.8, 95% CI 19.3–34.2) without a significant difference.

MR-proANP, MR-proADM, and CT-proET1 levels were significantly higher in women with PE as compared to controls, whereas the between-group difference in copeptin levels was marginal (table 1).

The effect of various clinical parameters on the study biomarkers is analyzed in table 2. PE was a significant and independent determinant of higher MR-proANP, MR-proADM, and CT-proET1 levels. Increased MR-proANP was also independently related to the administration of antenatal steroids, whereas increased MR-proADM was associated with multiple gestation and larger GA. Lower GA and lack of antenatal steroids were the only significant determinants of increased copeptin levels (table 2).

Logistic regression analysis revealed that MR-proANP, MR-proADM, and CT-proET1 were significant and independent predictors of PE (table 3). When all four biomarkers were included in a separate model, only MR-proANP and MR-proADM showed a significant association with PE (table 3).

MR-proANP presented the higher diagnostic performance (AUC 0.83; 95% CI 0.73–0.92), followed by CT-proET-1 (AUC 0.71; 95% CI 0.61–0.82), MR-proADM (AUC 0.64; 95% CI 0.52–0.76), and copeptin (AUC 0.62; 95% CI 0.50–0.73) (fig. 1). Since MR-proANP and MR-

Table 1. Characteristics of the study groups

	PE (n = 27)	Controls (n = 120)	p
<i>Maternal characteristics</i>			
BMI before pregnancy	23 (20/29)	22 (19/28)	NS
Nullipara	24 (89)	66 (55)	<0.001
Singleton	21 (78)	102 (85)	NS
Gestational diabetes mellitus	0 (0)	6 (5)	NS
Antenatal steroids (any)	17 (63)	29 (24)	<0.001
Age at delivery, years	36 (25/41)	32 (25/39)	0.034
GA at delivery, weeks	34 (27/37)	38 (32/41)	<0.001
Delivery vaginal	1 (4)	28 (48)	<0.001
<i>Infants characteristics</i>			
Male/female	16/11 (60/40)	71/49 (60/40)	NS
Birth weight, kg	1.7 (0.6/2.7)	3.0 (1.6/3.8)	<0.001
Small for GA	10 (37)	16 (13)	0.009
pH arterial umbilical cord	7.30 (7.2/7.4)	7.29 (7.2/7.4)	NS
Apgar 5 min	8 (6/9)	9 (8/10)	<0.001
<i>Biomarkers at triage</i>			
Copeptin, pmol/l	7.0 (2.0/42.0)	4.9 (2.1/14.7)	0.046
MR-proANP, pmol/l	157 (51/334)	67 (36/136)	<0.001
CT-proET-1, pmol/l	71 (49/101)	57 (41/85)	<0.001
MR-proADM, nmol/l	1.4 (0.7/2.3)	1.1 (0.5/1.9)	0.010

Data expressed as median (10th–90th percentile range) or number of cases (%). Statistical significance was assessed by Mann-Whitney U test, χ^2 test or Fisher's exact test, as appropriate. NS = Not significant (*p* ≥ 0.05).

proADM were related to PE independently of each other (table 3), the two biomarkers were combined (product of values). That biomarker index presented the highest diagnostic performance (AUC 0.88; 95% CI 0.79–0.96), albeit without statistically significant difference compared to MR-proANP alone (*p* = 0.176).

Discussion

In this prospective cross-sectional study, we analyzed quantitatively various promising plasma biomarkers of vasoactive peptides, namely copeptin, MR-proANP, CT-proET1, and MR-proADM in pregnant women at admission. The major finding is that by combining the two biomarkers MR-proADM and MR-proANP, a high diagnostic accuracy is achieved in specifically discriminating pregnant women with PE from controls at triage.

The results of this current study have important clinical implications, because the proposed marker combina-

Table 2. Dependencies of plasma biomarkers levels

	Copeptin		CT-proET-1		MR-proANP		MR-proADM	
	unadjusted	adjusted	unadjusted	adjusted	unadjusted	adjusted	unadjusted	adjusted
Nullipara	0.163 [‡]	0.037	0.183	0.154	0.189 [‡]	0.061	-0.024	-0.188
Singleton	-0.101	-0.067	-0.123	-0.027	-0.128	0.004	-0.139	-0.224 [†]
Preeclampsia	0.187 [‡]	0.125	0.272 [†]	0.220 [‡]	0.455*	0.269 [†]	0.217 [†]	0.363*
Gestational diabetes mellitus	-0.098	-0.032	0.036	0.096	-0.136	-0.042	0.122	0.130
Antenatal steroids	0.069	-0.388 [†]	0.195 [‡]	0.135	0.466*	0.277 [‡]	-0.078	0.146
Maternal age at delivery	-0.088	-0.159	0.083	0.083	0.184 [‡]	0.091	0.102	0.077
GA at delivery	-0.271 [†]	-0.513*	-0.151	0.062	-0.456*	-0.104	0.203 [‡]	0.479*
BMI before pregnancy	-0.077	-0.088	0.027	0.026	-0.023	-0.032	-0.099	-0.131

Data are adjusted regression coefficients obtained from simple linear regression models (unadjusted effect) and multivariable linear regression analysis (effect of each factor adjusted for the effect of the others). Biomarker levels are log-transformed. * $p < 0.001$; [†] $p < 0.01$; [‡] $p < 0.05$.

Table 3. Value of study biomarkers in diagnosing PE

	Model 1: copeptin	Model 2: CT-proET-1	Model 3: MR-proANP	Model 4: MR-proADM	Model 5: biomarkers only
Nullipara	0.013	NS	0.024	0.017	–
Singleton	NS	NS	NS	NS	–
Gestational diabetes mellitus	NS	NS	NS	NS	–
Antenatal steroids	NS	NS	NS	NS	–
Maternal age at delivery	NS	NS	NS	NS	–
GA at delivery	NS	NS	NS	0.013	–
BMI before pregnancy	NS	NS	NS	NS	–
Copeptin	NS	–	–	–	NS
CT-proET-1	–	0.022	–	–	NS
MR-proANP	–	–	0.013	–	<0.001
MR-proADM	–	–	–	0.002	0.012

Multivariable logistic regression analysis for assessing the diagnostic value of biomarkers after taking into account clinical confounders. The dependent variable in all models is PE. Data represent levels of significance (p values). NS = Not significant ($p \geq 0.05$).

tion may allow a fast and easy-to-implement identification of patients at risk for PE at triage and therefore may have the potential to reduce unnecessary admissions with increased monitoring, as well as lowering the number of misdiagnosed or unrecognized patients at admission, that may lead to severe maternal/fetal morbidity and mortality [6, 7]. Furthermore, the marker combination may help to reduce the number of inappropriate discharges as well as iatrogenic preterm deliveries.

Several markers have the promising perspective to be implemented in future clinical assessment of patients at risk for PE. Among them, blood biomarkers of angiogenesis are currently at the most advanced state of develop-

ment [3, 4]. Using the sFlt-1/PlGF ratio to diagnose PE, Verlohren et al. [16] demonstrated a high sensitivity and specificity with an AUC for all types of PE of 0.95 and for early-onset PE of 0.97. Whereas the predictive value for subsequent adverse outcomes in women admitted with suspected PE before 34 weeks' GA was found to be respectable when based on maternal arterial hypertension and proteinuria alone (AUC 0.84), it was significantly improved when the sFlt1/PlGF ratio was added (AUC 0.93) [17].

Compared to the AUCs found for the sFlt/PlGF ratio (ranging from 0.93 to 0.97) in identifying PE in suspected pregnant women, our here presented marker combination of plasma MR-proADM and MR-proANP dis-

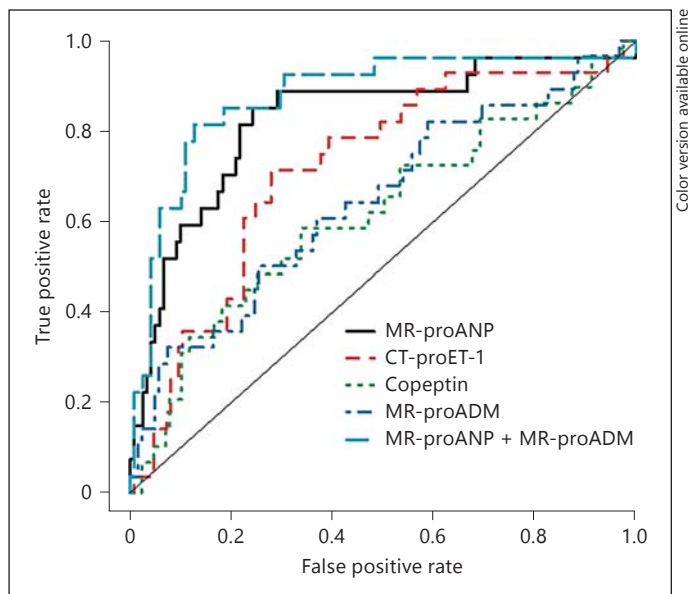


Fig. 1. ROC curves at triage for the diagnosis of PE of plasma biomarkers as indicated.

plays a similar AUC with 0.88 (95% CI 0.79–0.96). A recently published study found high sensitivity and specificity for MR-proANP alone with AUC of 0.85 (95% CI 0.79–0.90) in the discrimination of patients with PE versus controls close to delivery [18] which is in line with our findings of an AUC for MR-proANP alone of 0.83 (95% CI 0.73–0.92). The authors showed 3-fold elevated MR-proANP level in patients with PE as compared to normotensive controls, pointing towards high cardiovascular hemodynamic stress in PE, corroborating our data of more than 2-fold higher MR-proANP level in the preeclamptic group [18]. Accordingly, the degree of arterial hypertension has been found to be mirrored by plasma MR-proANP level in non-pregnant subjects [12, 19].

Apart from the hypertension marker MR-proANP, only MR-proADM increased the sensitivity and specificity in discriminating preeclamptic from control patients when combined with MR-proANP. Copeptin and CT-proET-1 did not contribute any added value in our model. So far, copeptin was investigated in just one study with PE and copeptin levels were found to increase markedly in parallel with the severity of PE when compared to women with normal, ongoing pregnancies of similar GAs in the third trimester [20]. In our study copeptin levels were also higher in the preeclamptic group (1.5-fold) but PE was not an independent determinant of higher copeptin in multivariable regression analysis.

In our study, the incidence of PE (18%) was higher as compared to about 5% in the overall population [1]. This is explained by the following two factors: (1) the ratio of high-risk pregnancies is usually higher at university hospitals, especially in the triage unit, as compared to the overall distribution, and (2) one important exclusion criterion of our study was regular uterine contractions during the first and second stage of labor. Hence, pregnant women presenting with commenced physiological labor were not included.

A limitation of our study was the time point of blood sampling in relation to the progress of PE. Furthermore, due to the cross-sectional design and enrollment of women at admission to the triage unit in order to establish diagnosis, the severity of PE varied. Therefore, additional trials are needed to prospectively investigate these markers in the second and third trimester of pregnancy up to the onset of manifest PE to assess the predictive value of these markers.

In summary, the current study shows that the combination of MR-proADM and MR-proANP might be a promising tool for risk stratification of pregnant women undergoing PE evaluation at triage. Whether both cardiovascular markers may help to identify pregnant women at risk for PE at early stage and whether both cardiovascular markers may add diagnostic information to the well-established angiogenesis biomarkers warrants further studies. On the whole, biomarker-assisted screening for PE appears to be a promising instrument in cost reduction [21].

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